December 9, 1958.

Dr. Joshua Lederberg
Department of Genetics
University of Wisconsin
Madison, Wisconsin

Dear Dr. Lederberg:

We really appreciate your penetrating comments on the manuscript
we sent you last summer entitled "The Direct Estimation of Mutation Rate
from Mutant Frequency Under Special Conditions." We were particularly im-
pressed by your comment that phenomic lag during exponential growth would
tend to impart an upward bias to the equilibrium mutant frequency. Actually,
we had considered this possibility in our own discussion but had rejected it
in terms of what now appears to be a misconception. We have generally looked
at mutation to respiration deficiency from the particulate loss point of view
and assumed that it was largely a pre-mutational loss (i.e. that it was more
probable that a bud with no particles would arise from a cell with one or a
few particles rather than from a cell with many). This view led us to infer
that the newborn mutant would be essentially incapable of phenomic lag divisions.
It is now apparent that this inference was based upon the assumption of
identity of particles bearing the respiratory enzymes, with particles con-
cerned with their synthesis.

Your comment stimulated us to reexamine the question and to attempt
to calculate the upward bias to the equilibrium mutant frequency if phenomic
lag did occur. If one assumes that every newborn mutant cell passes through
four phenomic lag generations, that respiratory capacity is equally partition-
ed at each division and that the growth rate with an obligately aerobic C
source depends upon respiratory capacity (i.e. the first phenomic lag gener-
ation takes the same time as a normal generation, and phenomic lag generation
time doubles in each successive generation) then one can calculate, either
by arithmetic or algebraic means, that the bias to the equilibrium frequency
is +78%. It turns out that these assumptions aren't particularly critical
so that assuming more than 4 phenomic lag generations does not affect the
estimate significantly. You may recall that our estimate of the error arising
from plating cells with attached buds was -40% so that these two errors are
in part compensating. We are incorporating some of this discussion into our
earlier manuscript.

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We were further stimulated to see if we could observe phenomic lag directly. The enclosed draft of a manuscript summarizes these experiments. We are still troubled by the possibility that the limited development, which we interpret as the direct observation of phenomic lag, might reflect a pre-mutational rather than a post-mutational event, (i.e. debilitated normal mother cells produce only mutant or debilitated normal offspring and then all debilitated normal cells mutate). Although reasonable arguments can be marshalled maintaining that this possibility is fairly unlikely, we would like to do a critical experiment to disprove it. At present we are discussing some micromanipulative bud stripping experiments to see if there is any evidence for a normal mother cell mutating in the strain which mutates at high frequency.

I know you are very busy but if you can spare the time to read the enclosed note and send us your comments we shall appreciate them. If time doesn't permit we shall understand.

The entire laboratory joins me in sending our congratulations on the Nobel Award.

Sincerely yours,

Maurice Ogur
Associate Professor
Biological Research Laboratory